

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA 21-113/N000BP suppl. amendment
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Bedford Laboratories
Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 5/4/01

Drug: pamidronate disodium injection

Drug class: bisphosphonate

Indication: treatment of moderate or severe hypercalcemia associated with malignancy with or without bone metastases.

Clinical formulation: 30 and 90 mg vials (10 ml) each containing: 3 or 9 mg pamidronate disodium, 47 or 37.5 mg mannitol, sodium hydroxide/phosphoric acid to pH 6-7.4, water qs 1 ml.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: The submission of this one month IV toxicity study in rats with pamidronate comparing an aged aqueous formulation (18 months) to a lyophilized formulation followed by a two month recovery was requested by DMEDP to address concerns about an uncharacterized — moiety. This apparent impurity may be present upon storage of the aqueous product.

Conclusions: The toxicity profiles of the aged aqueous and lyophilized formulations are identical. Minor difference occur in the incidence of some toxicities common to both formulations this probably reflects normal biological variation.

Reviewer signature:

cc: list: HFD-510/Davis-Bruno/Hedin

Studies reviewed within this submission: One month IV toxicity study comparing aged aqueous formulation to lyophilized pamidronate in rats.

Studies not reviewed within this submission: none

Introduction and drug history: The sponsor was requested to perform an additional toxicity study in an approvable letter dated 12/5/00 consisting of a one month toxicity study in rats with a 2 month recovery to address potential toxicities related to uncharacterized _____

TOXICOLOGY:

One Month IV Toxicity Study in Rats with Pamidronate: A comparison of aged aqueous formulation to a lyophilized formulation.

Key study findings:

Study no: 147-001

Volume #, and page #: 9.1, 1

Conducting laboratory and location: _____

Date of study initiation: 11/27/00

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: 2018-49-103679: _____

Formulation/vehicle: lyophilized pamidronate (Aredia) resuspended in 0.9% NaCl, aqueous pamidronate was diluted in sterile water

Methods (unique aspects):

Group Number	Group Designation	Dosage Level (mg/kg)	Dosage Concentration (mg/mL)	Dosage Volume (mL/kg)	Number of Animals	
					Males	Females
1	Control	0	0	2.22	15*	15*
2	Pamidronate, Aqueous	2	0.9	2.22	10	10
3	Pamidronate, Aqueous	20	9	2.22	15*	15*
4	Pamidronate, Lyophilized	2	0.9	2.22	10	10
5	Pamidronate, Lyophilized	20	9	2.22	15*	15*

* Five rats/sex/group in Groups 1, 3, and 5 were maintained for an additional 60 days with no treatment.

Dosing: The aqueous formulation used had been stored for 18 months (aged).

Species/strain: Crl:CD (SD) rats

Age: 8 weeks

Weight: males 189-255 g and females 158-210 g

Route, form, volume, and infusion rate: IV

Observations and times:

- Clinical signs: 2X daily
- Body weights: weekly
- Food consumption: weekly
- Ophthalmoscopy: not performed
- EKG: not performed
- Hematology: fasted prior to necropsy
- Clinical chemistry: fasted prior to necropsy
- Urinalysis: Day 30, 91
- Gross pathology: necropsy
- Organs weighed: adrenal, brain, heart, kidneys, liver ovaries spleen and testes

HISTOPATHOLOGY: Fixed tissues were delivered to _____ The following tissues were trimmed, embedded, and sectioned: adrenal glands, bone marrow (sternum), brain (brain stem, cerebellum, cerebrum), eyes (with optic nerve), femur (with articular surface), gross lesions, heart, injection site (last), large intestine (cecum, colon, rectum), small intestine (duodenum, ileum, jejunum), kidneys, liver, lungs (with bronchi), lymph nodes (mandibular, mesenteric), ovaries, pancreas, pituitary gland, prostate gland, salivary gland (mandibular), spine cord (cervical, thoracic, lumbar), spleen, stomach (forestomach, glandular), testes, thymus, thyroid/parathyroid (if present in section), uterus, and urinary bladder. Slides were stained with hematoxylin and eosin.

Histopathology was performed on all tissues from animals found dead, all tissues listed above from animals necropsied on Study Day 31, and the sternum, femur, kidneys, liver, lungs, spleen, thyroid, gross lesions, and injection sites from all recovery animals. The slides were evaluated microscopically by _____

Toxicokinetics: not performed

Results:

Mortality: Two unscheduled deaths. Male #9451 given 2 mg pamidronate lyophilized/kg was dead Day 11 with calculus within the urinary bladder and severe inflammation of the urinary tract consistent with obstruction of excretory ducts. Male #9487 (recovery group) was given 20 mg lyophilized pamidronate and found dead Day 22 with dilatation of the right kidney and enlarged thymus. This animal exhibited mild dilatation of the renal pelvis along with increased trabecular bone density in the femur and sternum. Mild inflammation was present at the injection site.

Clinical signs: unremarkable

Body Weight: unremarkable regarding formulations. Animals given 2 mg/kg had body weight gain decrements of ~20% and those given 20 mg/kg/day had ~30% regardless of formulation.

Food consumption: unremarkable

Hematology: unremarkable regarding formulations. Animals given 20 mg/kg pamidronate had a decrease (<10%) in mean corpuscular volume (M,F), hematocrit (F), hemoglobin (M,F) and increase (≥100%) in segmented neutrophils (M,F). These parameters were recoverable.

Clinical chemistry:

	MALES			FEMALES		
	Calcium	Phosphorus	Chloride	Calcium	Phosphorus	Chloride
Group 2 aqueous	↓8%	↓24%	↑6%	**	↓16%	**
Group 3 Aqueous	↓10%	↓20%	↑3%**	↓8%	↓17%	↑4%
Group 4 lyophilized	↓8%	↓19%	↑4%	↓7%	**	↑4%
Group 5 lyophilized	↓9%	↓18%	↑3%**	↓10%	↓21%	↑6%

** = No significant difference

The significant increase in chloride is attributed to the loss of concentrating ability of the kidney by the sponsor.

Urinalysis: elevation in hematuria in animals given 20 mg regardless of formulation or gender which was recoverable.

Organ weights:

Significantly Increased Spleen Weights						
	MALES			FEMALES		
	Absolute	Relative to Body Weight	Relative to Brain Weight	Absolute	Relative to Body Weight	Relative to Brain Weight
Group 3 Aqueous	62%	73%	59%	37%	50%	35%
Group 5 Lyophilized	52%	62%	51%	35%	44%	31%

A histological correlate for the increase in spleen weight was extramedullary hematopoiesis.

Gross pathology: unremarkable

Histopathology:

Summary of Treatment-Related Kidney Changes At the End of Treatment										
SEX	Males (Number=10)					Females (Number=10)				
GROUP	1	2	3	4	5	1	2	3	4	5
OBSERVATION	-	-	-	-	-	-	-	-	-	-
Tubular Degeneration	0	0	6	1	6	0	0	5	0	7
Average Severity*	0	0	1.1	0.1	0.8	0	0	0.9	0	0.9
Tubular Dilatation	0	6	7	8	4	0	0	4	0	1
Average Severity*	0	0.9	1.2	1.5	0.6	0	0	0.8	0	0.1

* Average severity based upon a grading scale where: 0 = normal, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe (marked).

At the end of the treatment period, treatment-related skeletal changes consisted of mild to moderately increased deposits of metaphyseal and/or epiphyseal bone (Diagnosed as *Hyperostosis, Metaphyseal and Hyperostosis, Epiphyseal*, respectively) in sternal and femoral bone sections. Although hyperostotic bone changes were present in both sexes given low and high-doses of the aqueous and lyophilized formulations, changes were moderately more severe in males. To determine a possible relationship between the thickness of proliferating metaphyseal bone and increasing dose concentrations of the test materials, the thickness of metaphyseal trabecular bone (spongiosa) was measured in a linear fashion from the growth plate (base) to the general region of termination (apex) in the marrow cavity of the metaphysis or diaphysis. The average thickness (mm) of metaphyseal trabecular bone in both the femur and sternum has been listed for each sex and dose group in the following table:

Average Thickness (mm) of Metaphyseal Trabecular Bone (Spongiosa)										
SEX	Males (Number=10)*					Females (Number=10)*				
GROUP	1	2	3	4	5	1	2	3	4	5
OBSERVATION	-	-	-	-	-	-	-	-	-	-
Femur (Hyperostosis)	1.55	6.15	6.90	7.11	6.40	4.10	4.25	4.83	5.10	4.61
Sternum (Hyperostosis)	0.0	0.52	0.57	0.60	0.55	0.0	0.23	0.23	0.26	0.25

* Number = 9 for Group 4 males and Groups 3 and 5 females

	Group 1		2		3		4		5	
	M	F	M	F	M	F	M	F	M	F
Kupffer cell hypertrophy					10/10	10/10			10/10	9/10
Triaditis					6/10	5/10			4/10	3/10
Thyroid follicular cell hypertrophy			1/10		4/10		1/10		2/10	
Injection site perivascular Hemorrhage	7/10	6/10	9/10	8/9	9/10	6/10	6/10	4/10	4/10	5/10
Injection site perivascular inflammation	1/10			1/9	4/10	5/10		1/10	4/10	8/10

Summary of individual study findings: Treatment related histopathology changes were observed in the kidney, liver, bone and injection sites of animals given aqueous or lyophilized formulations of pamidronate.

Tubular dilatation was characterized by focal clusters of cortical or medullary tubules with dilated lumens along with mild to moderate attenuation of epithelial lining. Occasionally dilated tubular segments exhibited small amounts of cellular debris or amorphous eosinophilic material. Dilated renal tubules were present in males at all dose concentrations however in females tubular dilation was restricted to HD groups and in both formulations. Tubular dilation was increased in the HD with the aqueous formulation compared to the lyophilized formulation in both males and females. Tubular degeneration was characterized by minimal to moderate diffuse contraction of tubular segments with inflammatory cell infiltrates and peritubular fibrosis. Rarely small clusters of necrotic tubular cells were present in degenerate tubules. Focal tubular degeneration is consistent with spontaneous nephropathy in male rats. The incidence and severity of kidney changes was similar with both formulations.

Metaphyseal trabecular bone was moderately increased in treated males and slightly increased in treated females. Thickness values were not increased in a dose dependent manner suggesting that proliferating trabecular bone was similar in both dose groups. The hepatic and splenic extramedullary hematopoiesis present in males given either formulation attributed to slightly reduced marrow hematopoietic compartments secondary to the proliferation of trabecular bone. The increase in splenic extramedullary hematopoiesis probably accounts for the increase in relative splenic weight.

Hypertrophy of sinusoidal Kupffer cells and minimal to mild inflammation of triad regions was observed at HD with both formulations. The pathologist report indicates an increase in liver triad inflammation with the aqueous formulation. Minimal to mild eprivascular hemorrhage was common at the injection site. Perivascular infiltrates of mixed inflammatory cells were slightly increased in animals given HD of both formulations with slightly greater incidence with the aqueous formulation.

Minimal hypertrophy of thyroid follicular cells with slight depletion of colloid was present in several treated males, but not in controls or females. This finding is consistent with mild physiologic stress and was not considered drug related by the pathologist.

The recovery animals (2 months) had prominent thickening and elongation of metaphyseal , trabecular bone (hyperostosis, metaphysis) of the sternum and femur with essentially no difference in the character and distribution of hyperostotic bone changes with either formulation. Renal dilation and degeneration along with hepatic and splenic changes were not observed in recovery animals.

Toxicology conclusions: The results of this study comparing aqueous (18 month old) and lyophilized pamidronate at 2 and 20 mg/kg for one month show identical toxicity profiles. Following a two month recovery period any histopathological changes were reversed with the exception of trabecular bone effects which were similar among the two formulations.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

(/s/

Karen Davis-Bruno

5/4/01 01:16:28 PM

PHARMACOLOGIST

no difference in toxicity profiles with aqueous vs. lyophilized pamidr
onate

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-113

Review Completed: August 5, 2000

Sponsor: Bedford Laboratories; 300 Northfield Road; Bedford, OH 44146

**PHARMACOLOGY REVIEW OF NDA
NDA 21-113**

DRUG: Pamidronate Disodium Injection;

CATEGORY: bisphosphonate

INDICATIONS: Treatment of moderate or severe hypercalcemia associated with malignancy with or without bone metastases, Paget's Disease

FORMULATION: 30 and 90 mg vials (10 ml)

Each ml contains:

3 or 9 mg Pamidronate disodium

47 or 37.5 mg Mannitol USP

sodium hydroxide/phosphoric acid to pH 6.0-7.4

Water qs 1ml.

BACKGROUND

NDA 21-113 (Pamidronate Disodium Injection) provides for a liquid form of Aredia® which will be used at the same dose as the currently available lyophilized form. For this new formulation, there are likely to be chemistry/stability issues and possibly biopharmaceutics issues related to the approval of this product. There have been no changes made in the current label regarding animal findings with the approved product. There were no pharmacology/toxicology studies submitted to this supplement.

The liquid formulation is associated with leaching of _____ from the glass container. The chemistry reviewer, Dr. Sheldon Markofsky, requested a pharmacology consult to assess the safety of levels of the leachables in the liquid intravenous dosage form.

SAFETY REVIEW

The table below summarizes the levels of the leachables in the 6, 9 and 12-month stability samples (taken from submission of 2-28-00, pp 58-59)

Concentrations of contaminants (PPM - range for 5 inverted stability samples)

	6 months	9 months	12 months	Product Release

a. ND = not determined

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

1 page

Recommendation:

The sponsor should be required to conduct a one-month rat intravenous toxicity study prior to approval. This should not significantly delay approval since there are still significant chemistry issues, which will take some time to address.

The iv rat study should evaluate drug product that contains the identified extractables , namely, product aged to the end of shelf life (18 months) We recommend that the study be designed with half the animals terminated at the end of the dosing interval and half remaining untreated for 2- months post dose prior to termination to assess for chronic granulomatous changes.

Draft Letter to Sponsor:

A one-month intravenous toxicity study in rats should be conducted to assess the safety of the extractables in your liquid pamidronate formulation. The study should evaluate drug product that has aged to the end of the shelf-life (18 months). We recommend that the study be designed with half the terminations for each dose group at end of dosing and half after a 2 month drug-free interval.

JSI

8/7/00

Jerri El-Hage, Ph.D
Pharmacology Team Leader

cc: NDA Arch
HFD510
HFD510/ElHage/Hedin/Markofsky
Review Code: AE
Filename: 21113.001.doc

HFD 10
APR - 1 1999

NDA 21-113

Review Completed: April 1, 1999

Sponsor: Bedford Laboratories; 300 Northfield Road; Bedford, OH 44146

**PHARMACOLOGY REVIEW OF NDA
NDA 21-113**

DRUG: Pamidronate Disodium Injection; Aredia®

CATEGORY: bisphosphonate

INDICATIONS: Treatment of moderate or severe hypercalcemia associated with malignancy with or without bone metastases.

FORMULATION: 30 and 90 mg vials (10 ml)

Each ml contains:

3 or 9 mg Pamidronate disodium

47 or 37.5 mg Mannitol USP

sodium hydroxide/phosphoric acid to pH 6.0-7.4

Water qs 1ml.

NDA 21-113 (Pamidronate Disodium Injection; Aredia®) provides for a liquid form of Aredia® which will be used at the same dose of the currently available lyophilized form. There are no new inactive ingredients in this formulation. For this new formulation, there are likely to be chemistry/stability issues and possibly biopharmacology issues related to the approval of this product. There have been no changes made in the current label regarding animal findings with the approved product. There were no pharmacology/toxicology studies submitted to this supplement. There is no need for further action from pharmacology.

RS
Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

4/1/99

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Hedin
Review Code: AP
Filename: 21113.001.doc